

Complement Biomarkers for C3G and Primary IC-MPGN



Assessment of complement biomarkers may reveal complement overactivation to aid in the diagnosis of C3G or primary IC-MPGN¹

Biomarker	Description	Reference Range	Observations and Implications in C3G/Primary IC-MPGN
Ba ^{2,3}	Cleavage product of factor B	<1.2 mg/L	Levels typically elevated
Bb ²⁻⁴	Active proteolytic enzyme of AP C3 convertase (C3b•Bb)	<2.2 mg/L	Levels typically elevated
C3 ^{3,5,6}	Central protein of the complement system. Activation of any of the 3 complement pathways results in C3 cleavage and subsequent downstream immune response	90-180 mg/dL	Levels typically low
C3b ⁵⁻¹¹	C3 fragment produced by cleavage of C3. Excessive deposition of C3 fragments occurs as a result of complement overactivation	Normal	Excessive C3b deposition in the kidneys
C3c ^{3,11,12}	C3 fragment produced by cleavage of C3. Excessive deposition of C3 fragments occurs as a result of complement overactivation	<1.5 mg/L	Levels typically elevated
C4 ^{3,13-15}	Cleaved to C4a (anaphylatoxin) and C4b (part of classical C3 convertase [C4b•C2b])	15-47 mg/dL	Levels typically normal, but may be low
C5 ^{3,16}	Cleaved to C5a (anaphylatoxin) and C5b (initiator of terminal pathway activation to form C5b-9)	13.5-27 mg/L	Levels typically low
Factor B ^{3,17}	Binds to C3b to form AP pre-convertase (C3b•B)	22-50 mg/dL	Levels typically low
Factor D ^{3,18}	Cleaves C3b-bound factor B, generating C3b•Bb and activating AP amplification loop	0.78-1.59 mg/L	Levels may be elevated
Factor H ^{3,19}	Critical regulator of AP activity	180-420 mg/L	Patients with factor H mutations may have reduced plasma factor H levels and/or function
Factor I ^{3,20}	Limits complement activation by cleaving C3b and C4b, preventing assembly of C3 and C5 convertases	18-44 mg/L	Patients with factor I mutations may have reduced plasma factor I levels and/or function
Fluid phase activity assay (IFE) ^{10,21}	Quantifies the conversion of C3 to C3 fragments	<7.5%	Aberrant levels can help determine if a protein in the blood is causing complement dysregulation/activation
Properdin ^{3,22}	Positive regulator of AP; binds to and stabilizes C3 convertase (C3b•Bb), prolonging its half-life	10-33 mg/L	Levels typically low
sC5b-9 ^{3,23}	Soluble pore-forming MAC; mediates irreversible cell lysis	<0.30 mg/L	Levels typically elevated

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Biomarker	Description	Reference Range	Observations and Implications in C3G/Primary IC-MPGN
NeFs/autoantibodies: Common drivers of disease that are present in 50%-80% of patients			
C3NeF (C3CSA); C5NeF (C3CSAP) ^{6,10}	Autoantibodies against C3 or C5 convertases that stabilize these enzymes	<20%	Common drivers of disease present in 50%-80% of patients; levels typically elevated
C4NeF ^{10,14,15,24}	Autoantibody against classical C3 convertase (C4b•C2b); stabilizes C4b•C2b and prolongs its half-life	<20%	Present in ≈3% of patients with C3G; levels typically elevated if present
Factor B autoantibody ^{3,10,25}	Binds factor B and/or Bb (of C3 convertase); enhances C3 convertase activity	<200 AU	Patients with factor B autoantibodies may have improper C3 convertase regulation
Factor H autoantibody ^{3,10,26}	Binds to and blocks N-terminal region of factor H, compromising its fluid-phase regulatory function	<200 AU	Patients with factor H autoantibodies may have compromised AP regulation
Functional assays			
AH50 ^{27,28,a}	Measures AP activity	77-159 units/mL	Abnormal values may indicate AP dysregulation
APFA ^{3,10,29}	Measures C9 neoantigens produced by C5b-9 activation; determines AP dysregulation	50%-130%	Levels may be low
CH50 ^{3,30}	Measures total hemolytic activity of classical and terminal pathways	41-95 units/mL	Levels typically low due to low C3 levels
WIESLAB ^{®31}	Enzyme immunoassay for assessment of complement functional activity	CP: Mean, 99% of PC LP: Mean, 49% of PC AP: Mean, 71% of PC	Values typically low

^aAlso known as AP50.

AH50, complement alternative pathway hemolytic assay; AP, alternative pathway; AP50, complement alternate pathway activation 50%; APFA, alternative pathway functional assay; AU, arbitrary units; C3CSA, C3 convertase stabilizing assay; C3CSAP, C3 convertase stabilizing assay with properdin; C3G, C3 glomerulopathy; CH50, complement hemolytic activity 50%; CP, classical pathway; FH, factor H; IC-MPGN, immune complex membranoproliferative glomerulonephritis; LP, lectin pathway; NeF, nephritic factor; PC, positive control.

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